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ORIGINAL ARTICLE

Dosing-time contributes to chronotoxicity of clofarabine in mice via means other than pharmacokinetics

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Abstract To evaluate the time- and dose-dependent toxicity of clofarabine in mice and to further define the chronotherapy strategy of it in leukemia, we compared the mortality rates, LD_{50}s, biochemical parameters, histological changes and organ indexes of mice treated with clofarabine at various doses and time points. Plasma clofarabine levels and pharmacokinetic parameters were monitored continuously for up to 8 hours after the single intravenous administration of 20 mg/kg at 12:00 noon and 12:00 midnight by high performance liquid chromatography (HPLC)-UV method. Clofarabine toxicity in all groups fluctuated in accordance with circadian rhythms *in vivo*. The toxicity of clofarabine in mice in the rest phase was more severe than the active one, indicated by more severe liver damage, immunodepression, higher mortality rate, and lower LD_{50}. No significant pharmacokinetic parameter changes were observed between the night and daytime treatment groups. These findings suggest the dosing-time dependent toxicity of clofarabine synchronizes with the circadian rhythm of mice, which might provide new therapeutic strategies in further clinical application.
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Introduction

Clofarabine, a second-generation nucleotide analogue developed in the late 1980s [1], has been used for the treatment of acute leukemia. It is a hybrid of cladribine and fludarabine, and possesses many advantages over the prototype drugs. It is lower in neurotoxicity, more stable in acidic solution and less susceptible to bacterial cleavage. All these characteristics promise better oral bioavailability and clinical safety [2]. Although originally used as a hematological malignancies curing agent, it is also efficient on many other solid tumors and has good therapeutic outcomes in elderly patients [3]. Available evidence suggests clofarabine inhibits tumor cell growth mainly via the inhibition of DNA synthesis, which eventually leads to apoptosis of cells [4–6], but also exerts cytotoxicity on normal cells. On one hand, clofarabine suppresses tumor cells in the rapid proliferative and static phases [4–5], on the other hand, it is indeed hazardous to the organs and body of humankind.

Efficacy and toxicity of drugs are largely affected by the circadian rhythm *in vivo* [7]. Thus, it provides us with a new strategy for drug therapies with narrow efficacy–toxicity dosage ratio, like most chemotherapy medicines. The optimal chronotherapy will augment efficacy and minimize toxicity of antitumor agents [8]. More than 40 available clinical chemotherapy drugs have been validated with obvious chrono-effects in rodents and humans [9–10]. Under a fixed delivery schedule, the tolerability of some conventional chemotherapy agents may rise by fivefold as compared with constant dosing-time regimen [11]. Another promising finding was noticed in independent trials, that is, the timing of best drug tolerability usually fits to best efficacy [12]. Therefore, research on the chrono-effects of drugs, especially for the toxic antitumor drugs, is urgent and meaningful, and the relevant findings will benefit clinical practice in the near future.

As a new generation antimetabolism tumor inhibitor, clofarabine is characterized by high stability and low toxicity on many tumors. However, clofarabine is usually distributed in many organs and cells, which certainly causes systematic toxicity, and sometimes the side effects are fatal. Our primary research indicated that the toxicity of clofarabine varied in the 24-hour period of 1 day, and optimal dosing-time of it may alleviate the instinct toxicity. However, there is no sufficient evidence to support this claim. Therefore, in this study, we observed the diurnal fluctuation of toxicity of clofarabine in 24 hours. We attempted to find out the relationship between toxicity and pharmacokinetic circadian rhythms of clofarabine in experimental animals, which might provide new chronochemotherapy regimen in future.

Experiments

Animal and reagents

Kunming mice (18–22 g, with equal numbers of male and female mice), were bought from Nanjing Qinglongshan Laboratory Animal Center (Certificate No.: SCXK 20080033). All these animals were housed individually in a strict 12-hour light/dark cycle and temperature-controlled (25 ± 2°C) environment with pelleted food and water *ad libitum*, and fed for 7 days to get used to the artificial diurnal variation prior to assays. This study was approved by the Animal Care and Use Committee of Wannan Medical College (Approval No. of Animal Care: WNYXY 2013-0284), and all the studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (US National Research Council 2011). Clofarabine was supplied by A-Tuo Chemical Co. Ltd (Nanjing, China). Aminoleucine transferase (ALT), aspartate aminotransferase (AST), creatinine (Cr) and blood urea nitrogen (BUN) quantitative determination kits were provided by Jianchen Biological Engineering Institute (Nanjing, China).

Acute toxicity assay

Mice were randomly divided into six groups (20 mice each). The different groups received intraperitoneal injections of clofarabine at the dose of 330 mg/kg at 8:00 AM, 12:00 noon, 4:00 PM, 8:00 PM, 12:00 midnight and 4:00 AM, respectively, each day. The treatments lasted for 7 days. After the first administration, the treated mice were observed continuously for abnormal reactions and mortality until the end of the assay. The circadian rhythm of acute toxicity of clofarabine at the same dose was analyzed using an observation based on the cosinor-based rhythmometry method [13].

Another 80 mice were randomly divided into four groups (20 mice each), and injected intraperitoneally with clofarabine at 8:00 AM, 12:00 noon, 8:00 PM and 12:00 midnight, respectively. Various doses (600, 480, 384, 307, 246 mg/kg) were adopted for every time point. After 7 days continuous administration, the Bliss method was used to calculate LD_{50}s of clofarabine at four different dosing-time points in a 24-hour period.

Subacute toxicity assay

One-hundred twenty mice were divided into two equal groups: 12:00 noon and 12:00 midnight administration groups respectively. Each group was then divided into three subgroups according to which treatment cycle they received (5, 10 and 15 days). Treated animals received an intraperitoneal injection of clofarabine at a dose of 50 mg/kg daily according to the predetermined arrangement. The same numbers of mice served as vehicle controls for each treatment group, and received the same volume of saline. During the observation period, the mice were observed intensely for food intakes, weight changes and abnormal reactions. By the end of the assay, the blood of the mice was collected into clean test tubes through the fossa orbitalis vein. A portion of the blood was treated by EDTA for the whole blood cell count, and another portion was used to separate serum for further biochemical analyses. Then all the animals were sacrificed. Main organs were promptly removed, weighed, and fixed in 10% formalin for histopathological examinations. Organ indexes of mice were assessed by the ratio of organ weight versus body weight (mg/10 g body wt.).

Sampling of plasma for pharmacokinetic assay

Mice were randomly divided into 14 groups ($n = 8$). Seven groups were injected intraperitoneally with 20 mg/kg of

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